GENERAL ANAESTHESIA FOR CAESAREAN SECTION IN SEVERE PRE-ECLAMPSIA

Comparison of the renal and hepatic effects of enflurane and halothane

J. A. CROWHURST AND M. ROSEN

SUMMARY

In a randomized study of patients undergoing Caesarean section, either enflurane (mean 0.24 MAC-h) or halothane (mean 0.23 MAC-h) and 50% nitrous oxide in oxygen were administered to women (n = 12) with severe pre-eclampsia-eclampsia and to 16 healthy pregnant patients with normal renal and hepatic function. No evidence of nephrotoxicity was found in any pre-eclamptic or normal patient. Metabolism of enflurane resulted in plasma inorganic fluoride concentrations (max 15 µmol litre\(^{-1}\)) which were well below the toxic value. Postoperative liver function tests showed no important changes from preoperative values, although reductive metabolites of halothane were not measured. In patients with severe pre-eclampsia there appears no contraindication to enflurane or, probably, halothane as volatile supplements during general anaesthesia.

Pre-eclampsia-eclampsia (PET) is a serious complication of pregnancy, present in up to 5% of deliveries (Hibbard and Rosen, 1977), and responsible for 10% of maternal deaths in England and Wales (Report, 1979). At least half of those mothers with PET require Caesarean section (Pritchard and Pritchard, 1975; Martin and Tupper, 1979; Akinkugbe and Coker, 1980) and form about 15% of all Caesarean sections. General anaesthesia is the most widely used method for abdominal delivery especially in severe PET, partly because of the possibility of coagulopathy (Davidson and Phillips, 1972).

Enflurane has suitable pharmacokinetic characteristics for use in obstetric anaesthesia and is satisfactory from a clinical point-of-view as a supplementary agent during Caesarean section in healthy patients (Coleman and Downing, 1975; Dick, Knoche and Traub, 1977; Marx et al., 1978). However, enflurane, like methoxyflurane, is metabolized to inorganic fluoride in man and there has been concern that, in theory at least, it may be nephrotoxic in patients with severe PET (Gutsche, 1979). However, this is unlikely since the metabolism of enflurane to inorganic fluoride is some 15 times less than that of methoxyflurane, and total dose is an important factor affecting nephrotoxicity (Cousins et al., 1976).

In this study, the renal and hepatic functions of normal mothers were compared with those of patients with severe PET following the administration of halothane or enflurane as supplementation during Caesarean section.

PATIENTS AND METHODS

Only patients with severe PET were studied. This was defined by Symonds (1979) as: arterial pressure greater than 140/90 mm Hg on two or more occasions, proteinuria of greater than 0.25 g/24 h (or ++++ on "dip-stick" testing) and non-dependent oedema. Patients were excluded who had cardiovascular, renal, hepatic or neurological disease, or who had received extradural analgesia, general anaesthesia or thiazide diuretics within the previous 3 months. As controls, patients without renal or hepatic disease undergoing elective Caesarean section were studied. Patients in the PET and normal groups were allocated randomly to receive either halothane or enflurane as supplementation to nitrous oxide anaesthesia.

The patients were interviewed before their operations (JAC) and agreement sought to enter the trial. Anaesthesia was induced with thiopentone 3–5 mg kg\(^{-1}\). Suxamethonium 1.5 mg kg\(^{-1}\) was given and the trachea intubated. Anaesthesia was maintained with 50% nitrous oxide and either 0.5% halothane or 0.8% enflurane delivered from pre-calibrated vaporizers (Cyprane type III) in oxygen. Tubocurarine chloride 0.3 mg kg\(^{-1}\) was given and artificial ventilation continued with a Manley ventilator (a non-rebreathing system) maintaining an end-tidal carbon dioxide concentration of approximately 4% (Beckman LB2 infra-red analyser).

At delivery, synthetic oxytoxin 10 units and morphine 5–10 mg were administered i.v. and the in-

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spired nitrous oxide concentration increased to 70%. Enflurane was continued at 0.4% and halothane at 0.5% (the lowest vaporizer setting) until the end of the operation when atropine and neostigmine were administered. Blood, i.v. fluid (lactated Ringer's solution) and protein replacement (plasma protein fraction) were administered as necessary.

Venous blood was collected before the induction of anaesthesia, and at 1, 2, 4, 8, 12, 24, 48 and 72 h after the end of anaesthesia. All specimens were centrifuged within 1 h of collection and plasma was assayed to determine the concentrations of sodium, potassium, calcium, bicarbonate, urea, uric acid, total protein, albumin, bilirubin, aspartate transaminase, alkaline phosphatase and inorganic fluoride.

Urine specimens were collected before operation, and in the early morning for 4 days following surgery. The osmolality, and protein and inorganic fluoride concentrations were determined for each sample.

Inorganic fluoride concentration was measured with an Orion fluoride-specific electrode pre-calibrated with horse serum containing known concentrations of inorganic fluoride over the range 0.1-60 μmol litre⁻¹. Blood samples from 25 normal mothers (34-40 weeks gestation) were used as controls.

Each patient received an intranasal “Desmopressin” test (0.4 ml of 0.1% solution) at midday on the 4th day after operation (after all i.v. fluid therapy had been stopped). Osmolality was determined on the second sample of urine passed after administration. This test of urine concentrating ability avoided the need for nocturnal fasting (Monson and Richards, 1978).

Statistical analysis

Logarithmic transformation was used to decrease the skewness and heterogeneity of variance. The data were then analysed with unpaired t tests, supplemented by Mann–Whitney and Fisher exact tests where required. Plasma inorganic fluoride concentrations were compared with analysis of covariance using the base-line value as a covariate since initial values varied from 0.10 to 11.0 μmol litre⁻¹, a range exceeding the increases in the postoperative concentrations.

RESULTS

The PET and healthy control patients (table I) were similar with respect to age, and although mothers who received enflurane were somewhat older, the difference was not significant. The mean systolic and diastolic pressures indicated severe PET in both the halothane and enflurane groups. Gestational age was greater in the control patients, but there were no significant differences between each normal or each PET group. The mean dose of enflurane or halothane was similar or slightly more, respectively, in the PET groups (table II). Apgar scores and time-to-sustained respiration (TSR) were used to assess the neonates (table III). The 1-min Apgar

### Table I. Clinical data. SAP = Systolic arterial pressure (mm Hg); DAP = Diastolic arterial pressure (Hg)

<table>
<thead>
<tr>
<th></th>
<th>Normal patients</th>
<th>PET patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Halothane</td>
<td>Enflurane</td>
</tr>
<tr>
<td></td>
<td>n  Mean SD</td>
<td>n  Mean SD</td>
</tr>
<tr>
<td>Max. antenatal SAP</td>
<td>8  126.9  12.3</td>
<td>8  126.3  9.2</td>
</tr>
<tr>
<td>Max. antenatal DAP</td>
<td>8  81.3  6.4</td>
<td>8  78.8  9.9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>8  27.8  3.9</td>
<td>8  30.4  5.1</td>
</tr>
</tbody>
</table>

### Table II. Mean doses (range) of enflurane and halothane administered

<table>
<thead>
<tr>
<th>Agent</th>
<th>Group</th>
<th>Dose (MAC-h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enflurane</td>
<td>Normal</td>
<td>0.20 (0.14–0.25)</td>
</tr>
<tr>
<td></td>
<td>PET</td>
<td>0.24 (0.20–0.24)</td>
</tr>
<tr>
<td>Halothane</td>
<td>Normal</td>
<td>0.20 (0.07)</td>
</tr>
<tr>
<td></td>
<td>PET</td>
<td>0.23 (0.11–0.56)</td>
</tr>
</tbody>
</table>
scores did not differ significantly between the anaesthetic agents, either in the normal patients or in those with PET. The difference in the 5-min Apgar scores between enflurane and halothane in the normal patients was significant ($P < 0.05$) using the $t$ test, but only approached significance using the Fisher test ($0.05 < P < 0.1$). Because of the non-specificity of Apgar scoring, this difference may not be clinically important. The TSR in each group of neonates were similar.

**Inorganic fluoride: plasma concentrations**

In 25 normal mothers (36–40 weeks gestation not having Caesarean section) the mean ($\pm$ SEM) plasma inorganic fluoride concentration was $2.64 \pm 0.34 \mu$mol litre$^{-1}$ which was within the range described for male surgical patients in the USA (Mazze, Cousins and Barr, 1974), but higher than the mean maternal concentration of $0.88 \mu$mol litre$^{-1}$ in Rochester (N.Y.) (Shen and Tares, 1974). Cardiff has fluoridated water and a high consumption of tea.

In the PET patients receiving enflurane, individual pre-anaesthetic concentrations varied from 0.1 to 11.0 $\mu$mol litre$^{-1}$ (table IV). Mean peak plasma fluoride concentrations were found to occur 1 or 2 h after anaesthesia in both normal and PET patients who received enflurane and were higher than in the halothane groups (fig. 1; table V). The highest individual peak value was 17.1 $\mu$mol litre$^{-1}$ in a normal patient who received enflurane and whose plasma fluoride concentration before operation was 2.3 $\mu$mol litre$^{-1}$. This patient was discovered subsequently to have taken chloroquine during her pregnancy and, as a result, was excluded from the series.

**PET patient No. 4 in the enflurane group** had a peak plasma fluoride concentration of 15 $\mu$mol litre$^{-1}$ at 2 h. This was the highest value obtained in the study, but her concentration before operation was 8 $\mu$mol litre$^{-1}$ (see also patient No. 3 in that group). The mean plasma fluoride concentrations before operation, of both groups of PET patients, were higher than those in the normal patients, although not significantly so. Analysis of covariance showed that each enflurane group had significantly higher fluoride concentrations than the halothane normal ($P<0.05$) and PET ($P<0.01$) groups for up to 8 h in the period after operation. There were no significant differences when normal and PET groups were compared either after enflurane or halothane when allowance was made for the fluoride concentrations before operation.

**Table IV. Individual plasma inorganic fluoride concentrations ($\mu$mol litre$^{-1}$) in PET patients receiving enflurane. *See text**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No. 1</td>
<td>0.1</td>
<td>2.1</td>
<td>1.7</td>
<td>1.5</td>
<td>—</td>
<td>1.5</td>
<td>0.9</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>6.1</td>
<td>7.0</td>
<td>7.0</td>
<td>4.1</td>
<td>4.6</td>
<td>3.7</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>3*</td>
<td>11.0</td>
<td>15.0</td>
<td>13.0</td>
<td>11.0</td>
<td>8.0</td>
<td>6.6</td>
<td>5.6</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>4*</td>
<td>8.0</td>
<td>10.4</td>
<td>15.0</td>
<td>8.0</td>
<td>12.0</td>
<td>11.2</td>
<td>10.0</td>
<td>8.6</td>
<td>6.2</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>11.4</td>
<td>9.6</td>
<td>10.2</td>
<td>11.0</td>
<td>10.4</td>
<td>7.0</td>
<td>5.5</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>5.0</td>
<td>4.6</td>
<td>4.9</td>
<td>5.2</td>
<td>1.8</td>
<td>1.8</td>
<td>1.6</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>9.1</td>
<td>9.2</td>
<td>8.7</td>
<td>8.1</td>
<td>2.8</td>
<td>4.2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Table III. Clinical data. TSR = Time to sustained respiration; *One neonatal death excluded. †Apgar score and TSR not recorded in one patient**

<table>
<thead>
<tr>
<th>Apgar score</th>
<th>Normal patients</th>
<th>PET patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>Halothane</td>
</tr>
<tr>
<td>1 min</td>
<td>8</td>
<td>8.6</td>
</tr>
<tr>
<td>5 min</td>
<td>8</td>
<td>9.5</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>8</td>
<td>40.1</td>
</tr>
<tr>
<td>TSR (min)</td>
<td>8</td>
<td>1.1</td>
</tr>
</tbody>
</table>
**FIG. 1.** Plasma fluoride concentrations (μmol litre⁻¹) in the four groups (PE = PET/enflurane; NE = normal/enflurane; PH = PET/halothane; NH = normal/halothane) between 1 and 72 h after anaesthesia (mean ± SEM).

**TABLE V. Mean plasma inorganic fluoride concentrations (μmol litre⁻¹)**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Normal patients</th>
<th>PET patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Halothane</td>
<td>Enflurane</td>
</tr>
<tr>
<td>n</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>---</td>
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<tr>
<td>0</td>
<td>8</td>
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<td>1</td>
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<td>2</td>
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<td>4</td>
<td>7</td>
<td>3.09</td>
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<td>8</td>
<td>7</td>
<td>3.75</td>
</tr>
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<td>12</td>
<td>8</td>
<td>3.41</td>
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<td>24</td>
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<td>48</td>
<td>7</td>
<td>2.59</td>
</tr>
<tr>
<td>72</td>
<td>7</td>
<td>3.50</td>
</tr>
</tbody>
</table>
Inorganic fluoride: urinary concentrations (fig. 2)

Peak urinary inorganic fluoride concentrations occurred on day 3 or 4 after surgery, in both the halothane and enflurane groups. The peak could not justifiably be related to plasma concentrations as urinary fluoride concentration is very dependent on pH which, by error, was not measured in every specimen (Barberousse et al., 1981). The peak value did not correlate with osmolality after desmopressin, also tested on day 4.

Renal function

Uric acid concentration (fig. 3). The hyperuricaemia which occurs with PET is readily apparent. There was a small increase in uric acid concentration after operation, with a tendency for the concentration to be a little lower in both enflurane groups for up to 4 h, but the differences were not significant. The profiles of changes with time were similar in both control and PET groups.

Urinary osmolality (fig. 4). Each patient had a urinary output greater than 10 mEq kg⁻¹ in the 12 h before the tests. Every patient concentrated the urine normally in response to desmopressin on the 4th day after operation. There were no important differences between the halothane and enflurane groups. There was no relationship between urinary osmolality and peak plasma inorganic fluoride concentrations.

Plasma electrolyte concentrations. Plasma sodium, potassium, chloride, calcium, phosphate and bicarbonate concentrations were all within their physiological ranges in all patients.

Plasma creatinine concentration (fig. 5). Creatinine concentrations were lower in the enflurane groups throughout. There were no significant differences between the increases in any group.

Plasma urea concentration (fig. 6). PET patients had higher urea concentrations than normal patients (P < 0.05) for up to 3 h after surgery. Although the values tended to be greater in the patients receiving halothane, the difference was not significant. There were no important differences between the two groups of healthy patients.
**Fig. 3.** Plasma uric acid concentrations (µmol litre\(^{-1}\)) in the four groups between 1 and 72 h after anaesthesia (mean ± SEM).

**Fig. 4.** Urine osmolality in the four groups.
Fig. 5. Plasma creatinine concentrations (μmol litre⁻¹) in the four groups between 1 and 72 h after anaesthesia (mean ± SEM).

Fig. 6. Plasma urea concentration (mmol litre⁻¹) in the four groups between 1 and 72 h after anaesthesia (mean ± SEM).
Hepatic function

Alkaline phosphatase concentration (fig. 7). Differences between the enflurane groups (up to 48 h) were significant, but not when adjusted for the initial values, and the differences between the two enflurane groups were consistent throughout the period of study.

Aspartate transaminase concentration (fig. 8). In general there was a small increase following surgery. In the healthy women the increase was greater after 12 h and higher in the healthy enflurane patients, but the changes were not significant. No correlation was found between the plasma transaminase concentration and the peak plasma inorganic fluoride concentrations.

Bilirubin. No patient recorded a plasma total bilirubin concentration of greater than 17 μmol litre⁻¹, the upper limit of the physiological range.

DISCUSSION

Enflurane has a low solubility in blood, with rapid uptake and elimination, and minimal biotransformation (2–4%) (Chase et al., 1971; Sakai and Takao, 1979) so that it is an attractive agent for obstetric anaesthesia (Coleman and Downing, 1975; Dick, Knoche and Traub, 1977). Furthermore, relaxation of uterine tone can be controlled more easily than with more soluble agents (Marx et al., 1978).

Women with severe PET, a condition with potentially serious renal and hepatic dysfunction, commonly receive general anaesthesia with a volatile supplement. Although the dose is small, the choice of anaesthetic has been empirical. No volatile agent has been studied specifically in mothers with severe PET, although Gutsche (1979) suggested that, theoretically at least, enflurane should be avoided. Halothane, although potentially hepatotoxic, has not been considered unsaf e.

Enflurane nephrotoxicity is a result of fluorosis of renal tubular mechanisms (Mazze, Calverley and Smith, 1977). Eichorn and colleagues (1976) have reported a non-pregnant patient in whom oliguric renal failure was caused by large-dose enflurane anaesthesia. This is unlikely, since fluoride-derived renal failure is high output, and enflurane has a clean record in patients with poor renal function (Carter, Heerdt and Acchiardo, 1976). In man, the toxic concentration of plasma inorganic fluoride which may result in nephrotoxicity is about 50 μmol litre⁻¹ (Cousins and Mazze, 1973), although a lower figure of 25 μmol litre⁻¹ (Mazze, Calverley and Smith, 1977) has been suggested. No PET

![Fig. 7. Plasma alkaline phosphatase concentrations (i.u. ml⁻¹) in the four groups between 1 and 72 h after anaesthesia (mean ± SEM).](image_url)
patient who had enflurane or halothane in this study approached even the lower "toxic" concentration. These results, therefore, fulfill the theoretical expectations that nephrotoxicity with enflurane is far less likely than with methoxyflurane (Cousins et al., 1976).

Fortunately, hepatic biotransformation of enflurane is virtually unchanged by enzyme-inducing drugs (Norgate, Sharp and Cousins, 1976; Allen and Downing, 1977), some of which may be used in the management of PET. Also, obesity, which is associated with PET, does not increase the metabolism of enflurane (Dundee et al., 1981).

Subclinical nephrotoxicity caused by fluoride may be detected by a vasopressin stimulation test of urinary concentrating ability; all our patients concentrated their urine normally. No correlation could be found between urinary osmolality after desmopressin and peak plasma inorganic fluoride concentration; the concentration test was performed at a time when peak urinary fluoride concentrations occurred in most patients.

Renal tubular function was assessed further by measurement of plasma uric acid concentration, which is increased consistently in PET and is an indication of the severity of the disease (Redman et al., 1976). In PET, the production of urate may be increased and destruction in the liver decreased, but renal excretion remains constant with approximately 80% of renal elimination attributable to secretion in the distal tubule (Chesley, 1978). Hamilton, Robertson and Campbell (1975) showed that hyperuricaemia in PET was increased when methoxyflurane was used during Caesarean section. Hyperuricaemia was a constant feature of PET in our patients, but there were no important differences between those patients receiving halothane and those receiving enflurane, providing further evidence that neither agent induced tubular dysfunction. Measurements of creatinine concentration indicated that glomerular function was unaffected.

Clinical testing of liver function in pregnant and surgical patients is difficult (Isselbacher and Lamont, 1980). Alkaline phosphatase concentration is increased in pregnancy as a result of hormonal effects, and the enzyme is, therefore, a less sensitive indicator of cholestatic or obstructive biliary pathology (Koff, 1980). However, the minor differences
between the control and the PET patients who received enflurane are unlikely to be of clinical importance.

Aspartate aminotransaminase concentrations increase commonly after surgical operations and can be related to the extent of the surgery (Clarke, Doggart and Lavery, 1976). In our healthy patients this increase occurred in the latter part of the period after operation, and was greater in those who received enflurane, but like bilirubin measurements, values remained within physiological limits.

Abnormal liver function in PET is associated with a decrease in liver blood flow (Koff, 1980). Cousins (1979) has suggested that toxic reductive metabolites of halothane may be found in similar circumstances; these should have been measured in the PET patients and are the subject of a further study. Although no contraindication to halothane for severe PET patients has emerged from this study, if there were concern, enflurane would be a useful alternative whenever liver function was abnormal (Black, 1979; 1982).

It seems reasonable to conclude that enflurane is a safe supplement to nitrous oxide in patients with severe PET.

ACKNOWLEDGEMENTS

The authors are grateful to their obstetric, midwifery and anaesthetic colleagues for their support. The authors also wish to thank Mr K. Tomlinson, Senior Chief MLSO of the Medical Biochemistry Department, Cardiff Royal Infirmary, for technical assistance, Miss Sara Marshall for preparation of the manuscript and Mrs Hazel O'Donnell for secretarial assistance.

REFERENCES


CAESAREAN SECTION IN PRE-ECLAMPSIA


ANESTHESIA GENERAL PARA CESAREAS CON SEVERA PRE-ECLAMPSIA

En un estudio al azar de pacientes sometidas a una operación cesárea, se administró enteral o de halotano (promedio 0.24 MAC-h) o de halotano (promedio 0.23 MAC-h) y nitrógeno el 50% en oxígeno a mujeres (n = 12) con severa pre-eclampsia y a 16 pacientes embarazadas sanas con función renal y hepática normal. No se encontró ninguna prueba de nefrotoxicidad en cualquiera de las pacientes pre-eclámpticas o normales. El metabolismo del halotano resultó en concentraciones de fluoruro inorgánico en el plasma (máx. 15 μmol litre^-1) que se encuentran muy por debajo del valor tóxico. Los ensayos postoperatorios sobre la función del hígado no demostraron ningún cambio con respecto a los valores preoperatorios, aunque los metabolitos reductores del halotano no se midieron. En pacientes con severa pre-eclampsia, no parece haber contra-indicación al halotano en cesáreas con severa pre-eclampsia.